REMARKS

Claims 28-39 and 48-55 are pending. Claims 28, 35, 36 and 54 have been amended, as follows:

Claim 28 has been amended to recite that each unit has the unit structure catalyst-substrate and that step b) involves the regeneration of the catalyst-substrate units. Support for this amendment is found throughout the specification and claims as originally filed.

Claims 35, 36 and 54 have been amended to correct typographical errors.

The specification has been amended to correct a number of typographical or grammatical errors.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. Objections to the Claims

Claims 35 and 36 are objected to as containing typographical errors. The typographical errors in claims 35 and 36 have been corrected.

Claim 54 is objected to as containing a grammatical error that does not allow meaningful interpretation of the claim. Claim 54 has been amended to address this issue.

II. The Rejection of Claims 28-39 and 48-55 under 35 U.S.C. 112, first paragraph

Claims 28-39 and 48-55 are rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement. The Examiner states that although the specification is enabling for the exemplified DNA polymerase and ligases, it does not reasonably provide enablement for any combination of any catalyst and any substrate.

The rejection is respectfully traversed. Applicants respectfully submit that the scope of the protection sought by the claims is commensurate with the scope of the enablement provided by the specification. The specification provides sufficient guidance for an artisan to carry out the claimed invention, including providing both general and specific guidance for constructing catalyst-substrate units. (See, e.g., the specification at page 9, lines 5-22, page 24, line 26 to page 25, line 13, and page 27, lines 5-23.) The specification also provides sufficient guidance as to how to carry out the substrate reloading step, including detailed guidance for selecting an appropriate reagents and conditions for this process step. (See, e.g., the specification at page 18, line 16 to page 24, lines 10.) The specification also provides a detailed

description for selecting and isolating a catalyst of interest from a library of catalysts. (See, e.g., the specification at page 33, line 11, to page 37, line 12.)

Applicants have also provided numerous representative working examples of each of the steps required to carry out the present invention, which demonstrate that one skilled in the art can practice the claimed invention commensurate in scope with the claims. (See Examples 1-9.) Although Applicants have not provided detailed examples for all embodiments of the present invention, Applicants are clearly not required to provide detailed examples of every working embodiment falling within the scope of the claimed invention.

Furthermore, any implication that the specification must teach a skilled artisan how to predict the sufficiency of each catalyst- substrate unit suitable for use in the present invention prior to actually producing and testing, is improper because it precludes the availability and necessity for routine testing. *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (noting that enablement is not precluded by the necessity for some experimentation such as routine screening.) The *Wands* court also recognized that the test for determining whether undue experimentation is required even permits a considerable amount of testing. *See id.* Thus, even though experimentation might be time consuming, it is the nature and not the amount of experimentation that is determinative of non-enablement. In this regard, although some experimentation would be required to apply the invention to some catalysts and substrates, the experimentation would not be considered by an artisan to undue.

In conclusion, the Examiner is improperly limiting Applicants' invention to the preferred embodiments exemplified in the Examples section of the specification. The Examiner's determination also does not accord proper weight to the guidance provided in the specification as a whole, the high level of skill in the art and the availability, under the enablement standard, of some experimentation.

Accordingly, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims under 35 U.S.C. 112, second paragraph

Claims 28, 29, 31-33, 48, 49 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The rejections are addressed as follows:

A. Claim 28 is rejected on the basis that the metes and bounds of the phrase "attached to at least one substrate" are not clear. The Examiner states that "attached to" can be interpreted to mean covalently attached, physically attached, in physically contact with, or non-

covalently attached, for example. The Examiner also states that it is not clear if "at least one substrate" means more than one molecule or more than one type of substrate.

As defined in the specification, the phrase "attached to at least one substrate" means a "direct or indirect physical connection." (See the specification at page 9, lines 5-9.) Thus, the phrase "attached to at least one substrate" is not indefinite as it is clearly defined in the specification.

As defined in the specification, the "substrate" is chosen according to the specific catalytic activity which will be selected. (See the specification at page 10, lines 4-13) The present invention and claims are not limited to the use of one type of substrate, and thus, the phrase "at least one substrate" can encompass "more than one molecule of the same substrate" or "more than one type of substrate."

Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Claim 28 is rejected on the basis that in the phrase "which converts said at least one attached product to at least one substrate so as to form said catalyst attached to said at least one substrate" is not clear, because it is not clear if the same or a different substrate is involved. As amended, the claims state that the recited conversion is "to regenerate said catalyst-substrate unit."

Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

C. Claim 28 is rejected on the basis that the term "reaction" is not clear. The Examiner asks if reaction means that the catalyst is a covalent catalyst that forms a covalent bond with the substrate or is an acid-base catalyst included even though no bonds are formed between the catalyst and the substrate.

The term "reaction" as defined in the claim (and as described in the specification) refers to the catalytic reaction between the catalyst and the at least one substrate. Thus, as used in claim 28, the term "reaction" is clear in that it broadly refers to the catalytic reaction between these recited entities, without limitation thereof on the type of catalytic reaction.

Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

D. Claim 29 is rejected on the basis that the term "biologically amplifiable" is not clear. The Examiner states that the specification (on pages 28-29) list examples of biologically amplifiable units, but that an artisan would not be able to determine if any DNA, RNA, peptide or

protein carrier system would be considered to be "biologically amplifiable" because DNA, RNA and proteins are encoded and can be amplified using biological means.

Applicants respectfully direct the Examiner's attention to the definition of "biologically amplifiable" provided in the specification on page 25-27. In particular, the specification states that that DNA, RNA and protein are all considered to be "biologically amplifiable."

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

E. Claim 31 is rejected as indefinite on the basis that term "flexible linker" is unclear. The Examiner alleges that the specification and claims do not provide a standard for measuring flexibility or required minimum flexibility provided.

The term "flexible linker" is both clearly defined and exemplified in the specification. (See the specification on page 27, lines 4-23.) Furthermore, the meaning of the term "flexible linker" and what flexibility is acceptable is well-understood in the art. (*See, e.g.*, Neri et al., WO 97/40141 (employing the term "flexible linker", on, e.g., page 34-36 (attached hereto as Exhibit A); *see also* U.S. Patent No. 6,369,199; U.S. Patent No. 6,326,166; U.S. Patent No. 6,387,626; U.S. Patent No. 6,309,645; U.S. Patent No. 6,281,344; U.S. Patent No. 6,074,639; and U.S. Patent No. 6,043,038).

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

F. Claims 32 and 33 are rejected as indefinite on the basis that the metes and bounds of the term "carrier system" are not clear.

Applicants respectfully submit that the specification clearly defines the term "carrier system." (See the specification on page 27, line 25 to page 29, line 10.) Applicants have also provided numerous examples of and referred the artisan to numerous scientific articles disclosing suitable carrier systems, which would further inform the artisan of the meaning of the term, as follows:

> Examples of biologically amplifiable carrier systems include (carrier system - catalyst molecule): phage - polypeptide (Boublik et al., 1995, Biotechnol (NY), vol. 13, pp. 1079-1084), filamentous phage - peptide (Kay , Winter and McCafferty, 1996, "Phage Display of Peptides and Proteins, A Laboratory Manual", Academic Press) , retrovirus - polypeptide (Buchholz et al., 1998, Nature Biotechnology, vol. 16, pp. 951-954), plasmid - peptide (Schatz et al., 1996, Meth. Enzym., vol. 267, pp. 171-191), polysome - peptide (Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA, vol. 91, pp. 9022-9026; He and Taussig, 1997, Nucleic Acids Research, vol. 25, pp. 5132-5134), bacteria - peptide

(Brown, 1997, Nature Biotechnology, vol. 15, pp. 269-272) and mRNA - peptide (Roberts and Szostak, 1997, Proc. Natl. Acad. Sci. USA, vol. 94, pp. 12297-12302), cDNA - peptide (analogous to the mRNA-protein fusion display, except that the protein has been attached to a cDNA of the mRNA that encodes it, rather than to the mRNA itself), peptide-secreting cell - peptide (Kinsella and Cantwell, 1991, Yeast, vol. 7, pp.445-454), peptide-secreting artificial microsphere - peptide (artificial microspheres containing proteins expressed from the genes contained within the microsphere, see Tawfik and Griffiths, 1998, Nature Biotechnology, vol. 16, pp. 652-656).

Examples of biologically non-amplifiable carrier systems include (carrier system - catalyst molecule): bead - organic molecule or bead - peptide (Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA, vol. 89, pp. 5381-5383), pin - inorganic molecule and bead - DNA sequence (Geysen et al., 1996, Chemistry and Biology, vol. 3, pp. 679-688).

Furthermore, the Examiner contends that the phrase "an entity comprising information allowing the unambiguous identification of the catalyst molecule of interest" is also unclear because the metes and bounds of the term "information" cannot be determined and what degree of certainty is required for an identification to be considered "unambiguous" is also not clear. However, the specification clearly defines and exemplifies what is meant by this phrase. (See the specification at page 10, lines 4-18). Furthermore, the term "unambiguous" is used in its plain an ordinary meaning and simply refers to the certainty of an artisan in identifying the catalyst of interest based on the information (e.g., DNA in a phage).

Accordingly, Applicants respectfully submit that the meaning of the metes and bounds of the term "carrier system" would be clear to an artisan. Applicants respectfully request reconsideration and withdrawal of the rejection.

G. Claim 28 is rejected on the basis that all of the catalysts catalyze the same reaction and that all of the substrates react to form the same product, but the claim does not appear to be limited in such fashion.

Contrary to assumptions underlying this rejection, the claims are not intended to limited to the same catalytic reaction. Indeed, the claimed method is applicable to both catalysts that have the same or closely related catalytic activities (such as, a variant protease library) or to catalyst that have different catalytic activities. (See, e.g., original claims 9 and 10.)

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

H. Claim 48 is rejected on the basis that it is not clear how it further limits claim 28 because claim 28 does not appear to allow for catalyst and substrate to be the same chemical substance.

Clearly, the catalyst and the substrate may be the same chemical substance, for example, an enzyme catalyst and a protein substrate are both classified as peptides. Conversely, the catalyst and the substrate may be different chemical substances, for example, an enzyme catalyst and a nucleic acid substrate. Claim 28 is not limited to the substrate and catalyst being only the same or only different chemical substances, but rather encompasses both situations. Thus, claim 48 further limits claim 28 in that it requires that "the catalyst and the at least one substrate are different chemical substances."

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

I. Claim 49 is rejected on the basis that the metes and bounds of "enriching" a library of peptides or polypeptides to obtain a "library of full-length proteins" are not clear. The Examiner states that it is not clear what methods are considered by applicant to be methods of enrichment. The Examiner also states that no method steps are provided that would result in full-length proteins, the origins of which are not defined.

Applicants respectfully submit that an artisan would clearly understand what is meant by the term "enriching" a library of peptide or polypeptides to obtain a full-length protein as this term is both defined and exemplified in the specification. The specification provides a description of what an enrichment process entails and why such process is beneficial. (See the specification at page 33, line 11 to page 34, line 29.) The specification also provides an example of various enrichment processes performed in preferred embodiments of the present invention. (See Example 1, page 44 and page 50, line 30 to page 53, line 18, Example 5 (describing enrichment of wild-type RNaseA) and Example 9 (describing a pre-enrichment process).)

Clearly based on these detailed examples and the description provided in the specification an artisan would understand what is meant by "enriching" a library of peptides or polypeptides. Applicants respectfully request reconsideration and withdrawal of the rejection.

J. Claim 54 is rejected on the basis that it includes a grammatical error that does not allow a meaningful interpretation of the claim.

Claim 54 has been amended to correct the grammatical error. Applicants respectfully request reconsideration and withdrawal of the rejection.

K. Claims 28, 30-33, 48 and 54 are rejected as indefinite on the basis that the term "substrate" is not clear. The Examiner states that a substrate is normally used only within the context of enzyme catalyzed reactions and not with reactions catalyzed by metals or small molecules.

The term "substrate" is clearly defined in the specification as the substrate for the catalyst, and is not limited to a substrate for an enzymatic catalyst. (See the specification on page 8, lines 17-26 and page 8, line 31 to page 9, line 11.) Although the term may generally be defined in textbooks in the context of enzyme activity, the use of the term substrate in the specification and claims is not inconsistent with at least its informal usage in the art. Accordingly, Applicants submit that the meaning of the term "substrate" is clear from both the context of the specification and the claims, and would be understood by an artisan to also refer to non-enzymatic substrates.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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Attorney Docket No.: 5655.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pedersen et al. Confirmation No: 7651

Serial No.: 09/390,851 Group Art Unit: 1627

Filed: September 7, 1999 Examiner: Prasthoffer, T.

For: Enzyme Activity Screen With Direct Substrate Reloading

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Sir:

Below is a marked-up version of the amendments made in the accompanying amendment.

IN THE SPECIFICATION:

The paragraph on page 19, line 21 to page 20, line 2, has been amended as follows:

Finally, in order to limit the time available to the catalysts for substrate turn-over, pulses of for example electricity or light may be applied during the selection. Appropriately separated pulses could create for example transient pH- or ionic gradients that would initiate the reaction substrate to product, performed by the catalyst. The pulses should be separated enough in time that it allows plenty of time for a catalyst in solution to become immobilized on a receptor before the [puls] pulse initiates the next reaction. In this way, the dead time of the selection performed in the column format (i.e. the time the catalyst spends diffusing from one receptor to the next) can be drastically reduced, and very high stringencies obtained.

The paragraph on page 20, lines 5-12, has been amended as follows:

For illustration, as a non-limiting example, [the] it is preferably in cases where the reagent(s) cannot efficiently act on the immobilized product, but only on the free product, the affinity of the column for the product must be adjusted to establish an appropriate equilibrium between the unbound and bound product. However, the optimal selection stringency is obtained if the reagent(s) act on both free product and product immobilized on column.

The paragraph on page 31, lines 3-14, has been amended as follows:

The term "library comprising nucleic acids having a number of different catalytic

activities" preferably denotes a library wherein said different catalytic activities are substantially different activities, e.g. nuclease, ligase, isomerase, phosphorylase. An advantage of such a library may be that by changing the substrate according to the specific activity of interest, said library may be used to identify a number of nucleic acids of interest. If for instance a DNA ligase of interest first is isolated by a method for in vitro selection as described herein by use of, *e.g.*, two DNA oligonucleotides as substrates, then a ribonuclease may be isolated thereafter by changing the substrate to, [a] *e.g.*, [a] an RNA oligonucleotide.

The title on page 34, lines 31-32, has been amended as follows:

Means of isolating an active [catalysts] catalyst of interest according to a method of the invention:

The paragraph on page 38, lines 28-30, has been amended as follows:

[The] The catalyst of interest is a SNase; the substrate is a single stranded oligonucleotide [(ssDNNA)] (ssDNA); and the product is the ssDNA cleaved by a SNase of interest.

The paragraph on page 55, lines 25-29, has been amended as follows:

This is an example of the selection scheme depicted in Figure 7. An [enzymes] enzyme with glycosidase activity is displayed on the surface of a filamentous phage using the principles [as] described in example 1 above and the skilled person's general knowledge.

The paragraph on page 55, line 30 to page 56, line 2, has been amended as follows:

The substrate is a glycogen linker substrate attached [on] to the surface of a filamentous phage using the principles [as] described in example 1 above and the skilled person's general knowledge.

The paragraph on page 58, lines 4-13,has been amended as follows:

The principle is here [examplified] exemplified in the case where the individual unit consists of a cell (bacteria or yeast), attached substrate (double stranded DNA with 5'-overhang), and secreted enzyme (ligase; for example, in a recombinant form that allows its secretion). A restriction enzyme (for example EcoRI) is used as the reagent. The selection is performed in the column format. The column matrix is coated with double stranded DNA with 5'-overhangs that are complementary to the overhangs exposed on the surface of the cell, and

that create an EcoRI restriction site upon ligation of the two DNA fragments.

IN THE CLAIMS:

Claims 28, 35, 36 and 54 have been amended as follows:

28. (Amended.) A method for identifying a catalyst of interest from a library of catalysts, said method comprising:

a) providing a library of catalysts comprising at least two different units, wherein each of said units comprises a catalyst attached to at least one substrate, each unit having the structure catalyst-substrate, wherein said catalyst is attached to said at least one substrate in a manner that allows a catalytic reaction to occur between said catalyst and said at least one substrate;

b) providing conditions suitable for said catalyst to catalyze the reaction of said at least one substrate to form one or more products, wherein at least one product of said catalytic reaction remains attached to said catalyst;

c) providing at least one reagent or condition which converts said at least one attached product to at least one substrate so as [to form said catalyst attached to said at least one substrate] to regenerate said catalyst-substrate units;

d) repeating said b) and c) at least once; and

e) selecting said catalyst with the desired catalytic activity.

29. (Unchanged.) The method of claim 28, wherein said catalyst is biologically amplifiable.

30. (Unchanged.) The method of claim 28, wherein said unit is biologically amplifiable and said catalyst and said at least one substrate attached to said catalyst are attached on the surface of said biologically amplifiable unit.

31. (Unchanged.) The method of claim 28, wherein said catalyst is attached to said at least one substrate by a flexible linker.

32. (Unchanged.) The method of claim 28, wherein said catalyst is attached to said at least one substrate by a carrier system.

33. (Unchanged.) The method of claim 28, wherein said catalyst is attached to said at least

one substrate by a flexible linker and a carrier system.

34. (Unchanged.) The method of claim 32, wherein said carrier system is a bead particle.

35. (Amended.) The method of claim 28, wherein said library of catalysts is a library [or] <u>of</u> peptides or polypeptides.

36. (Amended.) The method of claim 35, wherein said library of [peptide] <u>peptides</u> or polypeptides is a library of enzymes.

37. (Unchanged.) The method of claim 36, wherein said library of peptides or polypeptides is a library comprising recombined peptides or polypeptides.

38. (Unchanged.) The method of claim 36, wherein said library of peptides or polypeptides comprises shuffled peptides or polypeptides.

39. (Unchanged.) The method of claim 36, wherein said library of peptides or polypeptides comprises doped polypeptides.

48. (Unchanged.) The method of claim 28, wherein the catalyst and the at least one substrate are different chemical substances.

49. (Unchanged.) The method of claim 28, wherein said catalytic library of interest is a library of peptides or polypeptides, and said method entails prior to said a), enriching said library of peptides or polypeptides to obtain a library of full-length proteins.

50. (Unchanged.) The method of claim 29, wherein said selecting step is performed by immobilizing said product molecule.

51. (Unchanged.) The method of claim 29, wherein said selecting step is performed by immobilizing said product molecule to an affinity column.

52. (Unchanged.) The method of claim 29, wherein said selecting step is performed by

immobilizing said product molecule to a bead.

53. (Unchanged.) The method of claim 29, wherein said selecting step is preformed by immobilizing said product to a microchip.

54. (Amended.) The method of claim 29, wherein [said selecting step is preformed by the] said catalyst and the at least one substrate are bound to a matrix, and wherein said catalyst is released from said matrix when said at least one substrate is converted to said at least one product by said catalyst.

55. (Unchanged.) The method of claim 29, wherein said selecting step is preformed by providing a column having at least one receptor that is able to bind said at least one product.